Psychosocial variables and vaccination: a lifecourse approach

Phillips, Anna

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Anna C. Phillips

***Abstract*—** It is a widely held view that experiences and emotions can affect our health. However, only over the past twenty years or so has research shown how psychosocial factors such as stress, social support, and personality directly influence the body. The immune system was historically thought to act independently of other bodily systems, but it is now known that psychosocial factors can influence numbers of immune cells and even the function of the immune system. This paper will present contemporary evidence for an association between immunity and sources of chronic stress, social support, and personality using the antibody response to vaccination as a model. It will illustrate that the specific psychosocial factors which influence immunity, and thereby health, vary across the life course and act in synergy with ageing to influence the effectiveness of the immune system. .

***Keywords*—**immunity, stress, social support, vaccination.

I. Introduction

It is a commonly held belief that our social experiences, emotions, and aspects of our personality can influence our health. Most of us have experienced colds and other infections during stressful times in our lives. For example, a stressful academic schedule has been associated with meningitis infections in students [1], and the concept of mind-body interactions has led to research examining the links between, for example, mediation and immune cell function [2].

Historically, the immune system was thought to operate independently from the rest of the body, but it is now known that it shares close links with the nervous and endocrine (hormonal) systems. Such links were originally suggested by results from research conducted by Ader and colleagues in the late 1970's and early 1980's. In an elegant series of studies that the immune system is susceptible to classical conditioning [3]. For example, the repeated pairing of a neutral stimulus, saccharine, with an immunosuppressant drug in rats resulted in the animals showing immunosuppression in response to an antigen when presented solely with the neutral stimulus alone [4]. Subsequently, we have learned much from both animal and human studies about the intimate interactions between the nervous and immune systems and have increasingly come to appreciate the bidirectional nature of these links [5,6]. Such links provide the biological foundations for feasible physiological pathways through which our thoughts and feelings can directly impact upon our susceptibility to infection. Psychoneuroimmunology researchers aim to elucidate these pathways and establish their implications for health.

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II. Psychosocial factors and immunity

The relationship between psychosocial factors and immunity has received considerable attention over the past 30 years, with particular interest being directed at the association between psychological stress and the ability of the immune system to respond to infection. Early research focused especially on the influence of psychosocial stress on enumerative measures of immunity. For example, individuals exposed to chronic stress showed reduced numbers of B-lymphocytes [7,8], cytotoxic T-lymphocytes [7,9], natural killer (NK) cells [7,9] and lowered concentrations of secretory immunoglobulin A in saliva [10-13] compared to matched controls. In addition, persons suffering the chronic stress of separation/divorce showed lower numbers of T-helper cells than married individuals [14].

However, it is difficult to determine the clinical significance of such enumerative changes, given that such changes lie within the range of normal variation for healthy participants [15]. Changes in cell number may simply reflect lymphocyte migration and recirculation rather than increased production of cells. Additionally, cell number changes could be a consequence of shifts in plasma volume and haemoconcentration; in such circumstances, changes in cell number would reflect increased density of a lymphocyte population rather than signal a true increase in absolute cell numbers. In addition, even absolute changes in cell number might not necessarily reflect alteration in the capacity of the immune system to mount an effective response to antigenic challenge [15]. Consequently, measuring changes in cell

number is perhaps not the optimal means of determining variations in the functional capacity of the immune system, and hence the likely clinical implications of psychosocial variables for disease resistance and susceptibility.

In vitro measures of immune function, such as lymphocyte proliferation to mitogen and NK cell cytotoxicity, have been argued to provide a better indication of the functional capacity of the immune system [15]. These measures have been demonstrated to be susceptible to the influence of chronic stress [14,16-23]. Nevertheless, the isolated testing of any particular network of immune cells provides only limited information about the overall status of what is a highly integrated and complex system [15], and an imperfect understanding of the relationship between psychosocial factors and vulnerability to disease [24].

III. Vaccination

A clinically relevant model which examines the impact of psychosocial factors on the integrated response of the immune system to a challenge would avoid many of these disadvantages. Assessing the antibody response to vaccination provides one such model. Vaccines act as 'imitation' infections, through which we can measure how well the immune system responds to challenge, in terms of generating an antibody response.

The antibody response to vaccination involves the coordination of a wide variety of immune cells. The vaccine antigen is initially recognized and presented by professional antigen presenting cells, such as dendritic cells. The antigen is then recognized by specific T lymphocytes, which proliferate and differentiate into T-helper lymphocytes. Some vaccine antigen types are also recognized by B-lymphocytes without the necessity for antigen processing. When stimulated by an antigen, either alone or in conjunction with stimulation by T-helper lymphocytes, B-lymphocytes proliferate and mature into short lived plasma cells which produce the earliest antibody or immunoglobulin, IgM. In a primary response to an antigen not previously encountered, the peak IgM response occurs around five days after vaccination. Interaction between the activated T- and B-lymphocytes leads to the formation of germinal centers and then the production of high affinity IgG and IgA antibody. This response is slower than the IgM response, and reaches a peak around 28 days after vaccination. Secondary antibody responses, in which the immune system has been previously exposed to the antigen, are more rapid and of greater magnitude.

As such, the antibody response to vaccination gives an overall measure of how well the immune system responds to challenge and is both integrated and easy to interpret. It also covers the criteria of being clinically relevant, as variations in antibody levels are likely to reflect disease susceptibility and resistance. The most commonly investigated psychological factor in the context of vaccination is psychosocial stress, measured usually as life events exposure, perceived stress, or exposure to a particular chronic stressor, such as caregiving for a spouse with dementia.

The earliest studies using the vaccination model used novel non-pathogenic antigens to examine the antigen-specific antibody response. On days when participants reported high negative mood and negative life events, antigen-specific sIgA antibody levels to an oral rabbit albumin capsule were reduced; these levels were elevated on days when relatively high positive mood and positive life events were reported [25,26]. The primary immune response has also been examined using a novel protein antigen, keyhole limpet hemocyanin (KLH), which elicits a thymus-dependent antibody response. In one study of young women, the KLH-specific IgG antibody response was lower at eight weeks, but not three weeks, post-vaccination in participants reporting fewer positive life events prior to vaccination [27]. In contrast, in a more recent study, distress was observed not to be related to the development of anti-KLH IgG three weeks post-vaccination [28]. These data provide some evidence that the antibody response to a single antigenic exposure may be susceptible to psychosocial influence, although there is some inconsistency between studies.

IV. Younger adults

Studies of student samples, in which stress is usually assessed using a range of life events checklists and perceived stress measures, comprise much of the literature on the response to medical vaccinations. Such studies generally confirm that individuals reporting higher numbers of life events and/or greater perceived stress are characterised by poorer antibody status following a range of vaccinations including hepatitis B [29,30], meningococcal C [31], and influenza [32-34]. For example, in our own student study, individuals who reported greater numbers of life events in the past year and greater stressfulness of those events showed a poorer response to the B/Shangdong strain of the influenza vaccine. This was significant at both five weeks, $\beta = -0.35$, 95%CI = -0.04 to -

0.01, $p = 0.003$, $\Delta R^2 = 0.11$, around the time of the peak antibody response, and at five months, $\beta = –0.28$, 95%CI = -0.04 to -0.01, $p = 0.01$, $\Delta R^2 = 0.07$, where decay in antibody titre is often observed [34]. When using the clinical criterion of a four-fold increase in antibody response from baseline pre-vaccination levels, those with higher life event scores were less likely to be four-fold responders at five weeks, OR = 1.45, 95%CI = 1.02 to 2.06, $p = 0.04$, and at five months, OR = 1.77, 95%CI = 1.21 to 2.58, $p = 0.003$ [34].

An advantage of using the response to vaccination as a model of immune function is that the variation in inoculation schedules for certain vaccinations can be used to examine which particular aspects of the immune response may be vulnerable to psychosocial influence. For example, vaccination with an antigen to which the participant has not been previously exposed induces a primary antibody response. In contrast, vaccination against more common pathogens such as influenza, induce a secondary immune response which is more rapid and effective. By examining the effect of stress on both primary and secondary immune responses, we can begin to determine which aspects of the immune response are most susceptible to stress-induced modulation. Hepatitis B vaccination is useful in this context, as there is a low likelihood of prior naturalistic exposure to this pathogen, and the schedule consists of three inoculations over a six month period, thus incorporating an initial primary response and later secondary response to vaccination. The data in this particular area thus far are somewhat mixed, but there appears to be stronger evidence for a negative effect of psychological stress on the secondary response to this pathogen [24,35].

A further advantage to the vaccination model is that there are different types of vaccination, which can be used to help elucidate which cells involved in the vaccination response are influenced by psychological factors. Most vaccinations, which consist of inactivated or dead viruses like influenza, induce what is known as a thymus-dependent antibody response. In this type of response, the B cells, the makers of antibodies, require the help of T cells (matured in the thymus) in order to produce antibody. A few vaccinations, however, protect against bacterial infections or toxins like meningococcal A or tetanus respectively. The immune response against these pathogens does not require T-cell help in order to produce antibodies, and are thus termed thymus-independent vaccines.

A third type of vaccine exists in which substances that elicit a T-cell response are conjugated to a thymus-independent pathogen in order to boost the efficiency of the antibody response against the thymus-independent pathogen. Conjugate vaccines like meningococcal C induce a thymus-dependent response. If psychological factors are consistently associated with the response to thymus-dependent and conjugate vaccinations but not with thymus-independent response, this would imply that it is the T-cells that are particularly liable to psychological influence. Indeed, there is evidence to suggest that psychological factors like stress may exert their effects mainly on T-cells, as in one recent study higher frequency and intensity of stressful life events were associated with a poorer response to influenza and meningococcal C at five weeks post-vaccination, $\beta = –0.24$, 95%CI = -0.09 to 0.00, $p = 0.05$, $\Delta R^2 = 0.06$, but not to meningococcal A vaccination [34].

Similarly, in students we recently found that stress was negatively associated with the five-month response to the thymus-dependent hepatitis A vaccination, $\beta = -0.23$, $p = 0.03$, $\Delta R^2 = 0.05$, but not the thymus-independent pneumococcal vaccine, which was only associated with social support [36]. In addition, no association was found between stress and antibody response to a pneumonia vaccination in pre-school children [37]. However, as older care-givers have been reported to show poorer maintenance of antibody levels in the longer term following pneumonia vaccination than controls [38], it is possible that other factors such as age and severity of stress may interact to impair antibody-mediated immunity more generally than just the T-cell response.

V. Older Adults

The vaccination response in older adults has mainly been considered in the context of care-giving for a spouse with dementia. These studies have shown that caregivers have poorer antibody responses to vaccination in comparison to matched control participants [30,38,39]. However, this is a very specific stressor, and care-givers are likely to differ from the general population in ways other than the stress of care-giving, for example, in the amount of social support they receive.

Research examining the impact of more general psychological stress on antibody levels following vaccination is sparse. Nonetheless, it is important to study older adults in this context as they are likely to have different stress exposure histories than younger samples [40] and to have less efficient immune systems due to immune ageing or immunosenescence, which contributes to increased infectious disease susceptibility in older adults [41]. The effects of ageing on immune function may alter individuals' susceptibility to disease in part via a less efficient antibody response. One study found that older adults reporting higher perceived stress had lower antibody levels following influenza vaccination [42]. As baseline antibody

level prior to vaccination was not known, however, the impact on the actual response to the vaccine could not be assessed. More recently, in a study of 184 community-dwelling older adults, we observed that the stress of bereavement in the year prior to influenza vaccination was associated with a poorer antibody response to both A/Panama, $\beta = -0.15$, 95% CI = -0.30 to -0.02, $p = 0.02$, $\Delta R^2 = 0.022$, and B/Shangdong, $\beta = -0.21$, 95% CI = -0.34 to -0.09, $p = 0.001$, $\Delta R^2 = 0.040$, strains of the vaccine, [43]. Although overall negative life events exposure was not associated with vaccine response in this study, the effect for bereavement suggests that stress is related to pervasive immune effects throughout the life course, although the particular stressor of importance may change with age.

VI. Social support

The support of friends and loved ones may also be an important determinant of immune health. Studies assessing functional social support, a measure of the quantity and quality of social resources available to a person, have found that it is positively related to antibody levels following hepatitis B vaccination [30]. Similarly, there is evidence that feelings of loneliness and having a small social network size are associated with poorer influenza vaccination response [44]. In students we showed that a better quality of social support, particularly tangible support, was related to a greater peak, $\beta = 0.34$, 95% CI = 0.01 to 0.07, $p = 0.02$, $\Delta R^2 = 0.11$, and five-month, $\beta = 0.34$, 95% CI = 0.01 to 0.09, $p = 0.02$, $\Delta R^2 = 0.11$, antibody response to the influenza vaccine [34].

Interestingly, in a study described above, elderly caregivers, who showed greater deterioration in antibody protection against the thymus-independent pneumococcal vaccination than non-caregivers, also reported poorer social support [38]. Social support was also negatively correlated with pre- and post-vaccination titres against the A/Panama influenza strain yet positively with pre-vaccination antibody titres against the A/New Caledonia strain in elderly nursing home residents [45], a finding which even the authors were unable to explain. Further, among older adults, those who were married, and particularly those who were happily married, showed a better peak antibody response to the influenza vaccination than those who were unmarried or less happily married, $F(2, 95) = 4.94$, $p = 0.009$, $\eta^2 = 0.094$, [43]. Post hoc analyses indicated that participants who scored greater than the median in terms of marital satisfaction had higher 1-month antibody titers than both unmarried (mean difference = 0.29, $p = 0.002$), and less happily married (mean difference = .21, $p = .03$) participants, whereas the latter two groups did not differ from one another (mean difference = 0.009, $p = 0.32$). However, more general functional social support and social network size was not associated with antibody response in this older population [43]. These findings lend weight to the suggestion above that different factors become important, in terms of the influence on immunity, across the life course.

VII. Personality factors

Personality factors, although often examined in the context of health outcomes (see e.g., [46] have scarcely been investigated relative to the vaccination response. First, among a group of 12-year old girls who had not sero-converted prior to a live-attenuated rubella virus vaccination and were thus exhibiting a primary vaccine response, those characterized by higher internalizing scores, a concept linked to neuroticism, and lower self-esteem at baseline exhibited lower antibody titres following vaccination [47]. Similarly, in a study of female graduates and hepatitis, trait negative affect was negatively associated with the secondary antibody response to the second hepatitis B injection [48]. A related trait, neuroticism, was measured in undergraduate students, and was negatively associated with both the peak antibody response to the A/Panama strain of an influenza vaccination, and the maintenance of antibody titres to this strain; those with higher neuroticism scores had a poorer antibody response [49]. In contrast, dispositional optimism was measured in exercising and sedentary elderly individuals, but was not found to be associated with antibody titres following influenza vaccination [42]. Inconsistencies in results could be attributable to the different populations and the different measures of personality studied.

VIII. Synergistic effects of stress and ageing

The importance of the impact of studying different populations has been emphasised recently in studies of individuals undergoing the chronic stress of caregiving for a loved one. Studies in older adults have shown that caregivers have poorer antibody responses to vaccination in comparison to controls [30,38,39]. However, caregiving studies in younger populations are less conclusive [50] and in a recent analyses of our own within the West of Scotland Twenty-07 epidemiological study, only older, as opposed to younger or middle-aged, caregivers showed lower secretion rates of salivary antibody A in comparison to non-caregivers [51]. This raises the question of whether or not the chronic stress of

caregiving only becomes important for immunity when one is older, or whether it is the nature and extent of the caregiving burden which is important. We were able to address this question with a sample of parents of children with developmental disabilities, who are a younger population of caregivers reporting high levels of challenging behaviours in their children [52]. Recruitment focused on all developmental disability groups, but participants were parental caregivers of children with mainly Autism or Downs, and a matched parental control group from the local population. These individuals were vaccinated with both the pneumococcal and influenza vaccines and followed up one and six months later. Individuals who were caregivers were more likely to be non-responders to the pneumococcal vaccine than parents of typically developing children at both the 1-month (20% versus 4%) and the 6-month (48% versus 4%) follow-up, meaning that they were less likely to be able to mount a two-fold increase in pneumococcal antibody levels, $F(1,50) = 6.86$, $p = 0.01$, $\eta^2 = 0.121$, [53]. They also showed a poorer response to the B/Malaysia influenza vaccine strain at both time-points, $F(1,53) = 4.22$, $p = 0.04$, $\eta^2 = 0.074$ [54]. The antibody differences between the caregivers and non-caregivers were being driven by differences in their children's challenging behaviours in each case [53,54]. Further, within the caregiver group, those parents reporting higher numbers of challenging behaviours, particularly conduct behaviours, such as fighting other children, mounted the poorest antibody response [53,54]. This suggests that it is the stressful behaviour of the care recipient which determines effects on vaccination response. However, immune ageing may yet interact with this, as even in this restricted age range parental sample, there was a trend for younger caregivers to show the strongest antibody response ($p = 0.07$) [54]. This overall collection of evidence suggests that the immunologically worse off groups are those who have particularly challenging chronic stressors on top of immunosenescence.

IX. Clinical implications

The clinical implications arising from a better understanding of the varied relationships between psychological factors and the vaccination response are important, particularly in the context of older adults who already display increased susceptibility to disease. Psychological interventions to improve vaccination response in these populations could include techniques such as stress management, relaxation, cognitive behavioural therapy, and emotional disclosure. One study showed an improvement in the ability of older caregivers for a spouse with dementia to mount a four-fold increase in antibody titre following influenza vaccination relative to matched controls, although the mechanisms of effect were unclear [55]. Similarly, participants taking part in a written emotional disclosure intervention, where they wrote about their emotions about a previously undisclosed stressful event, showed significantly higher antibody titres at four and six months following vaccination with hepatitis B compared to a control non-intervention group [56]. However, Black individuals who wrote about their feelings and experience about racism in an emotional disclosure study showed poorer antibody titres to two out of three strains of an influenza vaccine relative to those writing about a neutral topic, although this may have been due to ambiguity about attributions of whether experience was due to racism or other factors [57]. Consequently, at this stage, the results are mixed, and much more work is required to establish what types of intervention are likely to be the most beneficial for psychological, and hence immunological, health in key at-risk populations such as older adults and caregivers.

Another potential clinical application of the vaccination model has arisen from the positive immune effects demonstrated in response to acute stress [58]. In students, an acute eccentric arm exercise protocol was applied six hours before giving an influenza vaccination in the exercised arm. The antibody response was assessed at six and 20 weeks post-vaccination, and interferon-gamma production in response to in vitro stimulation by the whole vaccine, an index of the cell-mediated response to vaccination, was assessed at 8 weeks post-vaccination. Eccentric exercise enhanced the antibody response in women, and the cell-mediated response in men [59]. This suggests that the development of such a behavioural challenge that could be applied in GP settings could be a way forward for improving the vaccination response. This would be particularly important for groups at risk of infectious disease such as older adults, the bereaved, and care-givers.

X. Conclusion

In conclusion, vaccination has had a substantial impact on public health, although not everyone mounts a satisfactory and protective antibody response to vaccination. This increasingly appears to be the case with progressing age. Studying antibody responses to vaccination is now contributing to the understanding of how psychosocial exposures can influence immunity and, consequently, resistance to disease. The current challenges are to unravel the underlying mechanisms and to develop and apply feasible behavioural interventions to

boost the response to vaccination and, thus, optimize our resistance against infectious disease.

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Dr Anna C. Phillips is a Health Psychologist. Her BSc (hons) degree in Psychology was completed at the University of Birmingham in 1998, she went on to work in psychological research and completed an MSc in Health Psychology at Staffordshire University, 2002. Her PhD in the Psychological factors associated with vaccination was completed in the School of Sport & Exercise Sciences, University of Birmingham, 2005.

She now holds a Roberts RCUK Research Fellowship at the University of Birmingham, School of Sport & Exercise Sciences where she has worked in research and taught Behavioural Medicine since 2005. Prior to her PhD, she worked as a research psychologist for Blackpool, Wyre & Fylde NHS Trust and the Health Services Research Centre, Coventry University. She has over 70 publications in the fields of behavioural medicine and psychoneuroimmunology. She is currently researching the interaction between psychological factors and immunity with a specific focus on ageing, as well as the health correlates of blunted cardiovascular reactions to stress. Dr Phillips is a member of the American Psychosomatic Society, Psychoneuroimmunology Research Society, British Psychological Society Division of Health Psychology, Society for Behavioural Medicine, and British Society for Research into Ageing. In 2010 Dr Phillips won two early career awards for her research from the American Psychosomatic Society and the Academy of Behavioral Medicine Research.